

TOXICOLOGY CONFERENCE IN GALVESTON, JULY 16-18, 1981

Dr. J. Ward discussed mutagenicity and mechanisms of carcinogenicity. Mutations occur at the molecular level in one of three ways: 1) base substitutions, 2) small base deletions or additions (frame-shift), and 3) by large base deletions. Cellular response to DNA damage was non-specific, dependent upon the area of DNA damaged. He also discussed the 2-stage model of carcinogenesis, mentioning that only a single low dose of the initiator is necessary for tumor formation in animals. Generally, the promoter needs repeated doses. All known mutagens are good initiators.

T. Conner discussed monitoring for environmental pollutants. These included the urine assay for mutagenicity, YFF sperm analysis, alkylation of macromolecules (looking for methylated histidine in hemoglobin).

Dr. Edward Reynolds talked about the effect of toxic chemicals on specific organ sites. He discussed Koch's Law as it relates to toxic chemicals. This is as follows:

1. The known prior exposure and agent must be present in the individual in whom the tumor develops.
2. It should produce the same disease in experimental animals under similar exposure conditions.
3. The agent or metabolites should be recoverable from the animal model in #2 in a manner which establishes a cause and effect relationship.

A discussion of intrinsic hepatotoxins versus host idiosyncrasy followed. With intrinsic hepatotoxins, the liver lesion was distinctive, time course predictable, incidence of toxicity after exposure high, dose dependency apparent, and the replication of lesions in experimental animals being present. The opposite was true with host idiosyncrasy. An example of idiosyncrasy was halothane, although there's some evidence in experimental animals that anoxia and chronic illness may predispose an individual to halothane damage. To show how careful one must be in evaluating epidemiological data, specific mention was made of increased liver cancer in the Gulf Coast area. He called this an epidemiological artifact when the pathologic specimens were examined. Out of 176 cases of supposed hepatoma, 54 proved to be primary liver cancer, 75 metastatic cancer, 27 had no cancer, and 20 had no supporting evidence for any disease.

Eric Comstock discussed clinical studies on asbestos workers. He made statements such as:

1. A study would be of little benefit to convince long-term asbestos workers to cease smoking as the latency period of the typical adenocarcinoma of the lung is 10-12 years and squamous cell carcinoma 6-8 years, indicating that they were already in the process of forming in many cases by the time the individual stopped smoking.
2. The mesothelioma rate of insulators was 18-20%. He did not explain his cohort or how the rate was derived (mortality statistics, etc.).
3. On post mortum exams, 70-100% of asbestos workers evaluated had some type of tumor in their lung.
4. As for the diagnosis of asbestos, symptoms and pulmonary functions tests were not very helpful; the best sign of asbestos was dry crackling rales listened for best along the posterior axillary line along the base of both lungs.
5. That oblique views of the chest were necessary for detection of lung cancer (probably his best statement).

Dr. J. Sherman discussed the role of physicians in identifying adverse chemical effects. The failure of physicians to recognize occupational diseases was highlighted. She then stated that any occupational carcinogen was not site specific. After giving us examples of what she called horror stories of cases that she has handled, she said that you will not find any cooperation among major industries. You will be hassled if you try to find out what is really wrong with the individual employee. After this talk, I could not restrain myself any longer. The challenge was made as to the question of site specific cancer in humans, citing BCME, benzene, hexavalent chrome, benzdine. I also recounted my history with Shell, telling her that I've never been hassled for looking into or investigating potential occupational injury or disease. A plea was made for the scientific approach to be used in the making of occupational diagnoses as in other aspects of medicine. Because of the lack of knowledge in the field, it is easy for one to draw assumptions rather than to operate according to logic and plausibility.

Janice Fabricant discussed effects of chemicals on the reproductive system. She mentioned a new study giving cyclophosphamide for 5 weeks to males, then mating them to females. The newborns from the females are then put through a battery of behavioral tests in an attempt to perhaps link future neurologic deficiencies to abnormal sperm.

Pat Buffler discussed the epidemiological approach to environmental agents. She mentioned a higher than expected lung cancer rate in the six counties of Texas that are heaviest in petrochemical industries. These were Harris, Galveston, Montgomery, Chambers, Jefferson, and Orange counties.

Dr. N. Trieff's topic was Cancer & Environmental Agents. He mentioned that chlorination of water can give rise to (chloroform) a potential human liver carcinogen. *Endonimics*

Dr. Sheldon Murphy discussed the chemistry of organophosphates as related to their toxicity. He also discussed treatment of the organophosphate poisonings. He pointed out that chronic peripheral neuropathies due to some organophosphates (i.e., leptophos) seem to be caused by an inhibitor of a neurotoxic esterase. He also discussed distal axonopathies as caused by N-hexane and MNBK. The active compound seems to be 2, 5 hexane-dione.

A question was raised as to chronic effects on personality of some of the organophosphates. He mentioned that there have been some individuals with demonstrated EEG changes and effects on memory that persisted.

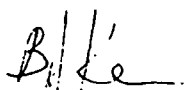
Dr. Joe Wagoner discussed specific histopathological lesions induced by environmental agents. Some of the points that he made were these:

1. As to the relationship of lung cancer to cigarette smoking, there is a definite dose response relationship with epidermoid cancer, less of a response with undifferentiated cancer, and no dose relationship demonstrated with adenocarcinoma of the lung.
2. With BCME and uranium mining small cell, undifferentiated carcinoma was increased in the majority of these individuals who did not smoke. Epidermoid and adenocarcinoma were also increased, but not as much.
3. Cadmium workers have $2\frac{1}{2}$ times the risk of developing lung cancer and $3-3\frac{1}{2}$ times the normal risk of developing prostate cancer.
4. VCM workers have an increased risk of developing large cell undifferentiated adenocarcinoma of the lung.

Dr. Pat Buffler challenged some of Dr. Wagoner's comments. She mentioned how the pathological classification of lung tumors has changed over the last 20 years, mentioning that systematic classification and pathologic review is necessary to insure correct epidemiological studies. She asked Dr. Wagoner if he had pathological review, and he responded that he did in 100% of the cases. This somewhat surprised Dr. Buffler who commented that she could only get them in 25% of the cases.

Our next talk was by Katherine Damme - Legal Problems in the area of Environmental Toxicology. She concentrated on cytogenetics for her remarks. If cytogenetics were done to weed out the genetically weak, this would cause legal problems. If you did not disclose results of cytogenetic studies to the individual, and he were to get cancer, you would be liable. If you did practice full disclosure, you lessen your chances of liability.

Marvin Legator closed the conference talking about the future developments in detecting adverse chemical effects. He discussed cytogenetic studies being used in the industrial setting, saying that they were available now and should be used. He said that the biggest problem chemical that we have right now is ethylene oxide. He mentioned what would be looked at in the next several years would be the list of the 76 known animal carcinogens.



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cc: CMD Physicians
Dr. James Sprawl, Monsanto Company